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Transient and executive function working memory in schizophrenia

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Abstract

Transient working memory requires attention and temporary storage of information, whereas executive function working memory requires additional mental manipulation of that information. Working memory impairment is common in schizophrenia patients, but only some studies have found differential impairment in executive function working memory compared to transient working memory. We measured both types of working memory using the Digit Span forward (DF) and backward (DB) tasks in a large sample of schizophrenia patients (n=267) and normal comparison subjects (n=82); in the patients, we also examined associations between performance on the Digit Span tasks and Letter–Number Sequencing (LNS), a putative executive function working memory test. Compared to healthy subjects, the schizophrenia patients showed impairment in the medium effect size range on both DF (d=−0.55) and DB (d=−0.68). DB scores predicted LNS performance, whereas DF scores did not. Worse negative symptoms were associated with worse performance on DF, DB and LNS. These results do not reflect differential executive function working memory dysfunction in schizophrenia, but appear to support transient and executive function working memory as separable constructs.

Keywords: Psychotic disorders; Cognition; Immediate memory; Short-term memory

1. Introduction

Working memory impairment is common in schizophrenia and has been proposed as a possible "core deficit" that contributes to multiple features of the disorder (Goldman-Rakic, 1994). Working memory is commonly defined as the capacity for "temporary *storage* and *manipulation* of the information necessary for such complex cognitive tasks as language comprehension, learning and reasoning" (Baddeley, 1992, p. 556, italics added). A recent re-conceptualization parses the storage and manipulation aspects of working memory by characterizing tasks as measuring either "transient online storage and retrieval" or "executive function working memory", respectively (Perry et al., 2001). The term "working memory" has been used inconsistently in the schizophrenia literature and elsewhere, but these more precise definitions should be useful in clarifying the findings of past and future investigations.

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The "transient" type of working memory is measured by "hold and repeat" tests in which the individual creates and maintains an internal representation of external stimuli. Examples of such tasks include repeating a series of digits, or holding a spatial location in mind and indicating the location following a brief delay. This latter type of task has been used by Goldman-Rakic (1994) and Park and Holzman (1992) to demonstrate transient working memory impairment in schizophrenia.

"Executive function" working memory is measured by tests that require transient working memory as well as additional processing or manipulation of the information held in mind. Common tests of executive function working memory include repeating digits in reverse order, pointing to a sequence of items in reverse order, and re-ordering a jumbled sequence of numbers and letters (Digit Span backward, Spatial Span backward and Letter–Number Sequencing from the Wechsler Adult Intelligence and Memory Scales (Wechsler, 1997a,b)).

Digit span tests are among the oldest in the history of psychology, appearing in some of the first widely used intelligence tests (e.g., the Binet-Simon Scale in 1905 and Wechsler's Bellevue Intelligence Examination in 1939; see Ramsay and Reynolds, 1995 for review). The Digit Span test purportedly measures both types of working memory. For the Digit Span forward (DF) items, the examinee is required to simply repeat, in order, a series of numbers read aloud by the examiner at the rate of one digit per second. For the Digit Span backward (DB) items, the examinee must repeat the series of numbers in reverse order. The DF and DB tasks become more difficult as the number of digits to be repeated grows longer. It has long been recognized that DF and DB are tasks that measure somewhat different abilities. DF requires reception, attention, temporary storage and repetition of the stimuli, whereas DB requires these abilities as well as manipulation (reordering) of the stimuli. Thus, DF appears to be a prototypical transient working memory task, whereas DB seems to measure ~~the~~ executive function working memory, because it demands manipulation of the items held in mind (Perry et al., 2001). (It should be recognized that, although DF does not involve re-ordering of items, there may be an "executive" component of successful performance on long digit span lengths, during which respondents often use a chunking strategy.) The difference in span between DF and DB (DIF) may also be a good measure of executive function working memory, because it controls for "hold and repeat" or transient working memory function assessed by DF. Presumably, greater DIF scores indicate more difficulty with the executive function component of working memory compared with transient working memory.

In a comprehensive review of the literature on digit span testing, Ramsay and Reynolds (1995) concluded that more investigations ($n=13$) supported separate scaling for DF and DB than supported combined scaling ($n=4$). Compelling evidence suggests that people often use visuospatial strategies to perform DB, but they rarely do so while performing DF (Ramsay and Reynolds, 1995). Brain imaging studies suggest that both tasks recruit left hemisphere brain regions, whereas DB appears to involve an additional right hemisphere substrate in the dorsolateral prefrontal cortex (Hoshi et al., 2000). Factor analytic studies, too, suggest that DF and DB often load on different factors (Ramsay and Reynolds, 1995).

Some investigations have found that patients with schizophrenia perform worse than healthy comparison subjects on both DF and DB (Conklin et al., 2000; Perry et al., 2001; Stefansson and Jonsdottir, 1996; Stratta et al., 1997); however, others have found that schizophrenia patients exhibit either no impairment on either test (Park and Holzman, 1992) or selective impairment in DB, but not DF (Stone et al., 1998). Many of these studies relied on small samples of 12–52 patients. A meta-analysis (Aleman, 1999) including 18 studies of DF and 7 studies of DB found no significant difference between the effect sizes comparing schizophrenia patients' performance to that of normal subjects ($d=0.71$ for DF and $d=0.82$ for DB). Evidence regarding the relationship between clinical symptoms, DF and DB performance have been mixed, with one study finding an association between severity of positive symptoms and poor performance on DF (Berman et al., 1997), and another study finding an association between severity of negative symptoms and poor performance on DB (Moritz et al., 2001).

In order to expand on the previous findings of smaller studies, we examined the relationships among DF, DB and DIF scores in a large sample of patients with schizophrenia and normal comparison subjects (NCs). We hypothesized that schizophrenia patients would perform worse than NCs on DF, DB and DIF, but would demonstrate a differential impairment on the measures more likely to tap executive function working memory, i.e., DB and DIF. We also sought to examine the associations of the Digit Span tests with a more challenging measure of executive function working memory (WAIS-III Letter–Number Sequencing), which requires reordering of both numbers and letters; our hypothesis was that performances on LNS would be more strongly associated with those on DB and DIF than DF. Finally, we examined correlations between psychiatric symptom severity and the various measures of working memory performance.

2. Methods

2.1. Participants and procedures

The present report is based on a secondary analysis of an existing dataset of schizophrenia patients and NCs who were enrolled in the University of California, San Diego (UCSD) Advanced Center for Interventions and Services Research. Data from 267 outpatients with either schizophrenia ($n=212$) or schizoaffective disorder ($n=55$) and 82 NCs who had completed the Digit Span tests as part of several parent studies, were used in the current study. Of the schizophrenia patients, diagnostic subtypes included paranoid (54%), undifferentiated (24%), residual (18%), disorganized (3%) and catatonic (<1%). Participants were recruited from San Diego County mental health providers, the UCSD Medical Center, the Department of Veterans Affairs San Diego Healthcare System and the San Diego community. Diagnoses of schizophrenia or schizoaffective disorder were made by the treating psychiatrist and confirmed via chart reviews using DSM-IV criteria or structured clinical interviews (e.g., Structured Clinical Interview for DSM-IV; First et al., 2002). The NC participants were screened for the absence of Axis I disorders with the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). Many participants have contributed data to previous studies from our research center. All parent studies were completed in accordance with the Declaration of Helsinki, with a complete description of the study to the subjects, who then gave written informed consent. This secondary analysis was approved by the UCSD Human Research Protections Program Institutional Review Board.

The NCs were demographically comparable to the schizophrenia patients with respect to age and education distributions. There were significantly greater proportions of women and non-Caucasians in the NC group. The participants were selected if they were 40–85 years of age and were determined by their treating psychiatrist to be sufficiently stable to undergo neuropsychological assessment. Subjects were excluded if they reported a history of head injury with ≥30-min loss of consciousness, history of seizure disorder, current diagnosis of dementia or current diagnosis of substance abuse or dependence as determined by their treating psychiatrist. Characteristics of the participants are summarized in Table 1.

Table 1
Demographic characteristics and cognitive test scores of study participants

	Schizophrenia patients ($n=267$) Mean (S.D.)	Normal comparison subjects ($n=82$) Mean (S.D.)	*t*	*df*	*p*
Demographics					
Age, years	56.42 (9.30) (range=43–85)	56.59 (10.13) (range=40–82)	−0.141	347	0.888
Education, years	12.60 (2.54) (range=5–20)	12.83 (2.27) (range=6–18)	−0.734	347	0.463
Age of illness onset, years	29.23 (13.14) (range=4–84)	–	–	–	–
Duration of illness, years	27.10 (13.30) (range=0–59)	–	–	–	–
SAPS	5.93 (3.59)	–	–	–	–
SANS	7.74 (3.97)	–	–	–	–
HAM-D 17	9.43 (5.88)	–	–	–	–
	Percentage	Percentage	χ^2		
Gender (% female)	32	68	34.63	1	<0.001
Ethnicity (% Caucasian)	76	57	10.81	1	0.001
% on no antipsychotics	18	–	–	–	–
% on typicals only	53	–	–	–	–
% on atypicals only	17	–	–	–	–
% on both	8	–	–	–	–
	Mean (S.D.)	Mean (S.D.)	*t*	*df*	*p*
T-scores					
DF	44.55 (10.36)	50.23 (10.26)	−4.35	347	<0.001
DB	43.50 (9.10)	50.05 (10.05)	−5.56	347	<0.001
DB *T*-score minus DF *T*-score	−1.05 (9.57)	−0.18 (7.83)	−.749	347	0.454
LNS ($n=61$)	39.05 (10.48)	–	–	–	–

A subsample of 61 patients was also administered WAIS-III Letter–Number Sequencing (LNS; Wechsler, 1997a), described below, by virtue of involvement in additional research studies. These 61 subjects had a mean age of 55.9 years (S.D. = 8.6) and a mean education of 12.5 years (S.D. = 2.7). Forty-two had schizophrenia (36% paranoid type, 33% residual type, 29% undifferentiated type and 2% disorganized type) and 19 had schizoaffective disorder. Forty-four percent were women and 72% were Caucasian; demographically, they were similar to the larger patient sample, except that a slightly higher percentage was women and there was a greater proportion of subjects with schizoaffective disorder. The patient groups with and without LNS did not differ significantly on their Digit Span scores (all t's < 0.4, all p's > 0.7).

2.2. Measures

Participants completed the WAIS-R or WAIS-III Digit Span task as part of a larger neuropsychological battery. These tests are identical except that the DF portion of the WAIS-III adds two trials of two digits, and the second trial of item 1 of DB is slightly different ("5–8" on WAIS-R versus "5–7" on WAIS-III). The first trials of DF are the easiest trials and all subjects were able to repeat at least three digits in the forward direction; therefore, two points were added to each subject's WAIS-R DF score to make the WAIS-R and WAIS-III scores equivalent.

As noted above, a subset of patients also completed LNS (Wechsler, 1997a), an abbreviation of a longer task developed by Gold et al. (1997) that requires the examinee to listen to a string of spoken letters and numbers and repeat back the numbers in ascending order, followed by the letters in alphabetical order. For example, if the examiner says "7-F-3-K-8-B", the correct response is "3-7-8-B-F-K".

Raw scores on DF, DB and LNS were converted into demographically corrected T-scores that control for age, gender, education level and ethnicity (Taylor and Heaton, 2001). A mean of 50 and a standard deviation of 10 apply to the standardization sample. To examine the DIF score, we subtracted the DF T-score from the DB T-score, so that higher numbers indicated better performance on the putative executive function working memory component of DB.

Patients were also administered the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984a), the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984b) and the 17-item Hamilton Depression Rating Scale (HAM-D 17; Hamilton, 1967). The total score on each instrument was used, with higher scores reflecting more severe symptomatology.

2.3. Data analyses

All the variables of interest were normally distributed in the NCs, the patients without LNS and the patients with LNS. Because the schizophrenia and schizoaffective disorder patients did not differ from each other on any of the Digit Span measures or on LNS (all t's < 1.2, all p's > 0.2), and have been shown to have similar cognitive profiles in previous research, we performed analyses on the combined patient sample. For the first hypothesis, independent samples t-tests were used to compare the mean digit span T-scores of the patients and NCs; Cohen's d effect sizes were calculated to quantify the magnitude of these differences. We used Pearson's correlations and hierarchical linear regression with raw scores to examine the second hypothesis. To explore associations between working memory performance and symptom severity, we computed Pearson's correlations between symptom ratings and working memory T-scores. All statistical tests were two-tailed, with significance levels set at 0.05.

3. Results

Our first hypothesis, that schizophrenia patients would show differential impairment on DB and DIF, as compared to DF, was not supported. The patient group performed significantly worse than did NCs on both DF and DB. However, the groups did not differ significantly on DIF (see Table 1). Effect sizes (Cohen's d) for group differences in the T-scores were $d = -0.55$ for DF, $d = -0.68$ for DB and $d = -0.10$ for DIF. The proportion of patients impaired (i.e., T-score < 40) on DF was 29.8%, whereas the proportion of patients impaired on DB was 26.4%. Only 12.3% of patients were impaired on DIF. The correlation between DF and DB was significantly lower in the schizophrenia subjects than in the NCs ($r = 0.52$ and $r = 0.70$, respectively, $Z = 2.28$, $p = 0.022$).

Our second hypothesis was that DB and DIF scores would predict variance in LNS scores, whereas DF would not be a significant predictor of LNS performance. In the subsample of patients ($n = 61$) who were administered LNS, 52.5% of participants were impaired (i.e., T-score < 40). There was a moderate correlation between LNS and DB ($r = 0.46$, $p < 0.001$) and a smaller correlation between LNS and DF ($r = 0.30$, $p = 0.019$), but the difference between these correlations did not

Table 2
Correlations between positive symptoms, negative symptoms, depressive symptoms and working memory performance

	HAM-D 17	SAPS	SANS
DF (n=243)	0.006	0.009	−0.156 *
DB (n=243)	0.090	0.062	−0.224 **
DIF (n=243)	0.078	0.047	−0.031
LNS (n=57)	−0.021	−0.009	−0.574 **

* $p<0.05$.
** $p<0.001$.

reach statistical significance ($t=1.39$, $df=58$, $p=0.170$). The correlation between LNS and DIF was low ($r=0.09$, $p=0.470$). In a hierarchical regression analysis predicting LNS scores, DF explained only 3% of the variance in LNS when forced into the equation first and was not a significant predictor ($\beta=0.181$, $p=0.162$). However, DB, entered second, explained an additional 9% of the variance in LNS and was a significant predictor ($\beta=0.354$, $p=0.019$).

We also examined correlations between depressive symptoms, positive symptoms, negative symptoms, and working memory performance (see Table 2). Depressive symptom and positive symptom scores were not associated with any working memory score. More severe negative symptoms were significantly associated with more impairment on DF ($r=-0.16$, $p=0.018$), DB ($r=-0.22$, $p=0.001$) and especially LNS ($r=-0.57$, $p<0.001$).

4. Discussion

Many previous studies (Conklin et al., 2000; Perry et al., 2001; Stefansson and Jonsdottir, 1996; Stratta et al., 1997) and a meta-analysis (Aleman, 1999) have found that participants with schizophrenia are about equally impaired on both DF and DB. Our results, using a large sample and demographically corrected *T*-scores, are consistent with these findings. Schizophrenia patients' average performance was slightly over half of a standard deviation lower than normative expectation for both DF and DB, suggesting only mild impairment in both transient and executive function working memory. The patients were not impaired on the difference between DF and DB, again suggesting that they are not differentially impaired on the executive function working memory component of DB.

Do DF and DB measure truly different abilities? Our results suggest that this is the case. When entered together into a multiple regression analysis, DB was a significant predictor of variance in LNS performance, whereas DF was not. The DIF score was not significantly associated with LNS performance and, as such, probably is not a good measure of the executive function component of working memory. Certainly, the reliability of DIF (or any difference score) is likely to be lower than either component of the score.

Worse negative symptoms were associated with poorer performance on DF, DB, and LNS, with the strength of the relationship increasing with increased working memory task burden. These results are consistent with those of Moritz et al. (2001) and others who have identified a relationship between neuropsychological impairment and severity of negative symptoms. Research utilizing data from neuropsychological testing, psychiatric rating scales and neuroimaging suggests that a frontal–subcortical substrate underlies both negative symptoms and neurocognitive impairment in schizophrenia (e.g., Sanfilipo et al., 2002).

An advantage of this study is the large sample size used to evaluate the main hypothesis. Limitations to this study include the relatively smaller patient subgroup that had been administered LNS and the lack of additional measures of working memory against which to compare the Digit Span tasks. There were also gender and ethnicity differences between the schizophrenia group and the NC group, although our use of demographically corrected *T*-scores controlled for those differences. Because we chose to match participants on age and level of education, it is possible that matching on education produced a sample of "underperforming" normal participants. Arguing against this possibility is the fact that our NC group performed exactly according to normative expectation on both DF and DB, using norms based on the large national standardization sample for the WAIS-III (*T*-score means of 50 and S.D. of 10; see Table 1).

Working memory, and particularly executive function working memory, has been considered important in the cognitive profile of schizophrenia. Although these results, along with previous findings, call into question the notion of working memory as a core deficit in schizophrenia, tests of working memory are commonly used to evaluate treatment outcomes, particularly in trials of antipsychotic medications. These findings suggest that DF and DB may measure different aspects of working memory (i.e., transient storage and executive functioning, respectively) and should be considered separately.

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